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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/665,552	09/22/2003	Johannes Bartholomaus	029310.50777CP	6176

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EXAMINER	
TRAN, SUSAN T	

ART UNIT	PAPER NUMBER
1615	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/665,552	BARTHOLOMAUS ET AL.	
	Examiner	Art Unit	
	Susan T. Tran	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-28 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12, 16-23, 41 and 42 of U.S. Patent No. 6,558,701 ('701). Although the conflicting claims are not identical, they are not patentably distinct from each other because the '701 patent claimed a multilayered tablet comprising a tramadol layer which contains tramadol or a pharmaceutically acceptable salt thereof, a diclofenac layer which contains diclofenac or a pharmaceutically acceptable salt thereof, and a separating layer which separates the tramadol layer from the diclofenac layer. Salts of tramadol and diclofenac are found in claims 2-4. The amounts of tramadol and diclofenac are found in claims 7-12. The

amounts in percentage weight if converted to weight ratios would fall within the claimed weight ratios. Controlled release matrix is found in claim 16. Coating polymer is found in claims 18-21. Granules, microcapsules or pellets of tramadol and diclofenac are found in claims 22 and 23. Accordingly, the present claims anticipated the claims of the '701 patent.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oshlack et al. US 6,077,533, in view of Raffa EP 0 546 676 A1.

Oshlack teaches a multiparticulate product comprising beads of immediate release active core coated with an extended release coating (abstract; and column 6, lines 8-38). Extended release coating comprises the claimed polymer (column 10, lines

1-67). Extended release coating can be applied as a layer to the immediate release core, or as a controlled release matrix (columns 12-13; and column 14, lines 1-2). Oshlack further teaches the claimed release profile (column 9, lines 23-46). Active includes tramadol, and nsaid such as diclofenac sodium (column 5, lines 12-25).

Oshlack does not teach the combination of tramadol and diclofenac.

Raffa teaches a composition comprising tramadol in combination with a non-steroidal anti-inflammatory drug (nsaid) (abstract). Tramadol includes salt of tramadol, such as tramadol hydrochloride (page 3, lines 31-32). Nsaid includes diclofenac (page 4, line 11). Raffa further teaches the claimed ratio between tramadol and nsaid (page 4, lines 19-24). Thus, it would have been obvious to one of ordinary skill in the art to modify the composition of Oshlack using combination of tramadol and diclofenac in view of the teaching of Raffa, because Raffa teaches combination of tramadol and diclofenac provides synergistic analgesic effects, because Raffa teaches combination employs lesser amounts of both drugs, which produces less opioid side effects such as abuse liability, tolerance, constipation and respiratory depression (abstract; and page 3, lines 11-19), because Oshlack teaches a desirability to obtain an effective opioid analgesic dosage form with the use of tramadol as an active drug, and because Oshlack teaches an oral dosage form of opioid analgesic which is bioequivalent and minimizes the food effect (columns 2-3).

Response to Arguments

Applicant's arguments filed 05/11/07 have been fully considered but they are not persuasive.

Applicant argues that the subunits of the present invention comprising tramadol and diclofenac randomly admixed in the final oral administration unit (e.g., hard gelatin capsules, tablet; see above). In contrast, as is evident from the disclosure of the '701 patent, the tramadol and diclofenac layers which are separated by a separating layer are ordered rather than being randomly distributed in the final multilayer tablet. These distinct features of the final oral administration unit (ordered vs. random design) affect the release profile of the active compounds. Taken together, the multilayer tablet of the '701 patent and the oral administration unit of the present application exhibit significantly distinct release profiles of the active substances.

However, in response to applicant's argument that the reference fails to show certain feature of applicant's invention, it is noted that the features upon which applicant relies (i.e., subunits comprising tramadol and diclofenac are randomly admixed to result in certain release profile) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Further, it is noted that the '701 patent does teach the subunits recited in the present claims. See for example claim 22 of the '701 patent, wherein the tramadol or diclofenac is formulated into granules, microcapsules or pellets is taught.

The statement "the multilayer tablet of the '701 patent and the oral administration unit of the present application exhibit significantly distinct release profiles of the active substances" is not clearly understood because the '701 patent clearly discloses the exact release profiles as required in the present claims 27 and 28 (see claims 41 and 42 of the '701 patent).

Accordingly, the double patenting rejection is maintained.

Applicant argues that Oshlack does not describe an oral dosage form where two active ingredients are provided, each in their own subunit, as is presently claimed. Instead, in Oshlack, the active ingredient is sprayed to coat inert beads and either the coated beads are inserted into a gelatin capsule (Example 1-3) or the coated beads are coated a second time with an extended release formulation and then inserted into a gelatin capsule (Examples 4 and 5). Even assuming that Oshlack were modified so that two active ingredients were provided, there is nothing to cause one of skill in the art to provide those two active ingredients in separate subunits. Moreover, on the present record there does not appear to be any reason that one of skill in the art might try to combine two active ingredients in a dosage form such as is taught by Oshlack.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir.

1986). Oshlack is cited in view of Raffa for the teaching to combine tramadol and diclofenac, because Raffa teaches combination of tramadol and diclofenac provides synergistic analgesic effects, because Raffa teaches combination of the two active agents employs lesser amounts of both active agents, which produces less opioid side effects including abuse liability, tolerance, constipation and respiratory depression (abstract; and page 3, lines 11-19). Oshlack teaches the use of tramadol or diclofenac, each in a subunit dosage form such as coated beads or coated multiparticulates. Thus, in view of the teaching of Raffa, it would have been obvious to one of ordinary skill in the art combine the subunit dosage form of tramadol with the subunit dosage form of diclofenac to obtain the claimed invention.

Applicant argues that Raffa considers diclofenac or a pharmaceutically acceptable salt thereof as a possible active ingredient, it does so only in an extensive list of NSAIDs (see Raffa, page 3, line 50 to page 4, line 15). Raffa does not disclose that diclofenac is a preferred active substance for the preparation of a pharmaceutical composition. In contrast, propionic acid derivatives and especially ibuprofen are described as preferred active substances (see, Raffa, page 4, lines 14-15). No examples including diclofenac and/or its pharmaceutically acceptable salt are not disclosed in Raffa (see page 4, line 50 to page 6, line 52, Examples 1-3). Only the selections tramadol-HC1/ibuprofen, tramadol- N-oxide/ibuprofen and 0-desmethyltramadol/ibuprofen are explicitly described (see Raffa, page 4, line 50 to page 6, line 52, Examples). Raffa does not indicate that the active substances tramadol and

diclofenac should be formulated separately to achieve desirable release profiles and bioavailability. Further, Raffa does not even consider the possibility that mixtures of tramadol and diclofenac could lead to poor solubilities for the active substances, thereby resulting in low bioavailability. The inventors of the present application determined, however, that in a conventional tablet comprising the active substances tramadol-HCl and diclofenac-Na, the solubility of both substances diminishes significantly (see present application, Figure 2). Raffa appears to fail to recognize the problem of the formation of sparingly soluble compounds which arise from the direct combination of tramadol and diclofenac. Although Raffa teaches the claimed ratio between tramadol and NSAID, the reference fails to recognize the possibility of undesirable solubility effects of tramadol and diclofenac, considering only compositions comprising tramadol material and the NSAID ibuprofen. Although Raffa teaches that a composition comprising a tramadol material and an NSAID displays synergistic analgesic effects, this teaching does not consider the undesirable solubility effects resulting from merely mixing the active substances tramadol and diclofenac. These undesirable solubility effects lead to an undesirable release profile (compare Figures 1 and 2 of the present application).

However, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208

USPQ 871 (CCPA 1981). In response to applicant's arguments that Raffa does not disclose that diclofenac is a preferred active substance for the preparation of a pharmaceutical composition, it is noted that Raffa is not limited to what the reference described as its' own inventions or to the problems with which it is concerned. A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including *nonpreferred embodiments*. Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.). At page 4, line 11, Raffa suggests combination of tramadol and diclofenac is possible and provides synergistic effect useful for the treatment of pain. Accordingly, it would have been obvious to one of ordinary skill in the art to modify the pain relief composition of Oshlack to combine tramadol with an NSAID including diclofenac.

In response to applicant's argument that Raffa teaches the claimed ratio between tramadol and NSAID, however, the reference fails to recognize the possibility of undesirable solubility effects of tramadol and diclofenac, considering only compositions comprising tramadol material and the NSAID ibuprofen. Although Raffa teaches that a composition comprising a tramadol material and an NSAID displays synergistic analgesic effects, this teaching does not consider the undesirable solubility effects resulting from merely mixing the active substances tramadol and diclofenac. These undesirable solubility effects lead to an undesirable release profile (compare Figures 1 and 2 of the present application).

It is noted that the present claims do not require the features upon which applicant relies (i.e., solubility effects between the combine drugs). Regarding the

release profile, applicant's attention is called to Oshlack at column 9, lines 23-46. It is further noted that applicant attempted to argue against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Raffa was not cited for the teaching of the claimed release profile.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan T. Tran whose telephone number is (571) 272-0606. The examiner can normally be reached on M-F 6:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SUSAN TRAN
PRIMARY EXAMINER

AU 1615